Salivary cortisol in children with cognitive impairment. [IF 2.1]

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Letters to the editor

'Facial naevus flammeus with choroidal haemangioma and without intracranial involvement'

SIR–We would like to report a male patient who was noted at birth to have left-sided facial naevus flammeus (port wine stain) involving the left side of the scalp, upper eyelid, and the left side of the nose. Follow-up in the next 6 years did not show any developmental problems, focal neurological deficit, nor seizures. His left eye was found to be hyperaemic over the bulbar conjunctiva. He also had anisometropic hyperoptic astigmatism of the left eye. Fundal examination confirmed the presence of left choroidal haemangioma, mainly in the upper half and posterior pole of the choroid. It was a well circumscribed lesion, slightly raised, bright red in colour, and affecting the left foveal region. The child had no evidence of raised intraocular pressure. The latest follow-up assessment at 6 years recorded visual acuity of 6/5(right eye) and 6/9 (left eye) with glasses correction. He is currently undergoing treatment for left amblyopia.

At 18 months of age the child had brain CT which was normal. To clarify the diagnosis further, and to be in a position to give the parents an accurate diagnosis and prognosis, MRI was performed at the age of 6 years. Brain imaging enhanced by gadalinium – DTPA was performed. This showed diffuse enhancement of the choroid with choroidal angioma of the left eye. There was no intracranial abnormality.

Naevus flammeus can be an isolated birthmark or it can be associated with ophthalmological and/or neurological abnormalities. When neurological abnormalities are present the diagnosis of Sturge-Weber syndrome (SWS) is highly likely. Stevenson and colleagues reported ocular findings in 50 patients with naevus flammeus.[1,2] Only one patient was found to have clinical evidence of choroidal haemangioma and this patient did not have intracranial abnormalities. Sullivan and coworkers reported the ocular manifestations of SWS in 51 patients. Of these, 28 had choroidal haemangiomas.[3] Choroidal haemangiomas in SWS patients are usually diffuse, primarily related to the posterior pole, and usually seen as red, flat to moderately elevated masses. This is in contrast to choroidal haemangiomas not associated with SWS which are usually discreet raised structures arising from the choroid.[4] In our patient, the naevus flammeus involves the ophthalmic and maxillary divisions of the trigeminal nerve and the choroidal haemangioma has the characteristics of those seen in SWS. However, the child does not have any neurological deficit.

We feel it is appropriate in these cases to clarify the possibility of intracranial involvement with neuroimaging to be able to give parents an accurate prognosis.

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'Salivary cortisol in children with cognitive impairment'

SIR–Cortisol plays an essential role in stress-regulation in humans.[1] It is produced in a well-defined circadian rhythm which is under the influence of an individual's sleep–wake activity. Under basal conditions, cortisol levels are highest in the early morning and subsequently decrease, reaching a minimum level after midnight. Gunnar and colleagues have provided evidence that in healthy children the cortisol circadian rhythm should be present at 15 months of age.[2]

Rises in cortisol levels may be a useful indicator that a person is experiencing pain.[3] This may be especially helpful in children with profound cognitive impairment (PCI) who may be unable to express themselves verbally.[4] To be able to recognize and interpret changes in cortisol levels in reaction to stressful events, the availability of reference values for stress- and pain-free children is essential. These reference values are available for normally developed, healthy children[5] but it is not known whether they are comparable with the levels typical of children with PCI and can, therefore, be used as normative data in studies of such children. Given the numerous, potentially painful events that can occur in children with PCI, and the almost complete lack of well-validated pain measures, these baseline data are urgently needed. The aim of this study was to provide baseline cortisol levels for children with PCI and compare them with levels in children without cognitive impairment. The medical ethical committee of the hospital approved this study and informed consent was obtained from parents of participating children.

There are two important reasons why diurnal cortisol levels in children with PCI may be disturbed. First, children with PCI usually have many physical problems. Second, although empirical evidence is lacking, clinical impressions indicate that children with PCI tend to show disturbed sleep behaviour.

Using a cross-sectional design, saliva samples were collected at 7.30, 12.30, and 17.30 in 49 children (29 males, 20 females; age range 1 to 18 years) with PCI and in 44 age- and sex-matched children without cognitive impairment. Origins of the cognitive impairment in the children with PCI were

documented (Table I). Cortisol levels were determined by radioimmunoassay. Interassay variation was below 14%, whereas intra-assay variations were between 5 and 7%, with the exception of samples with cortisol levels below 2nmol/L, where it was 16%. Sensitivity of the assay was 0.8nmol/l.

For both groups of children in this study, possible confounders of the measured cortisol levels were noted. Use of medication, especially analgesics and anticonvulsants,[6] was evaluated for both groups because of its influence on cortisol production. Thirty-nine children (41.9%; all cognitively impaired) had mild to severe epilepsy for which they were treated with a wide variety of anticonvulsant drugs. However, no stressful events or overt epileptic features occurred within the 2 hours before sampling. None of the children used analgesics on a regular basis nor used them on the day of sampling.

The Mann-Whitney *U* test ($p<0.05$) was used to compare median cortisol levels in saliva from the children with and without cognitive impairment. Fisher's exact test ($p<0.05$) was performed to investigate whether the difference in lack of a circadian rhythm in both groups was statistically significant. In order to test if children with cognitive impairment with and without a circadian rhythm of cortisol differed in clinical, physiological, or sociographic parameters, a Mann-Whitney *U* test was performed.

Cortisol levels and their circadian variation in children with cognitive impairment were not significantly different from those of children without cognitive impairment, although across all measurements the median cortisol levels for the cognitively impaired children were on average 0.5 nmol/L higher and showed more variation. When looking at the intra-individual variation of cortisol levels, in more than one third of the impaired children (40.8%) and in almost one third of the children without cognitive impairment (31.8%), a circadian rhythm was lacking. However, this difference did not reach statistical significance. Despite analysis of possible confounding variables, no explanation for the absence of a circadian rhythm was found. Technical problems such as the sensitivity threshold of cortisol levels were ruled out.

Table I: Origin of cognitive impairment (*n*=49)

Origin of cognitive impairment	*n*	*%*
Congenital/metabolic anomalies		
Syndrome	9	18.4
Infections	2	4.1
Major structural cerebral abnormalities	5	10.2
Total	16	32.7
Cognitive impairment during birth		
Perinatal asphyxia	7	14.3
Posthypoxic encephalopathy	5	10.2
Total	12	24.5
Cognitive impairment after birth (2 months – 2 years of age)		
Encephalopathy	11	22.4
Myocardial infarct	1	2
Meningo- or pneumococcal sepsis	5	10.2
Total	17	34.6
Origin remained unknown		
Total	4	8.2

Our results indicate that reference values of salivary cortisol in normally developed, healthy children can also be used for children with PCI. These data contain baseline, stress-free cortisol levels in children with PCI which can be used as a reference. In this way it is feasible to try and detect distress, or pain by measuring salivary cortisol levels in children with PCI in conjunction with pain assessment instruments developed for this group of children.[7] We are currently studying postsurgical cortisol levels of these children in order to gain insight into the relationship between salivary cortisol concentrations and nonverbal behaviour during painful episodes.

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